REMARKS/ARGUMENTS

Claims 1, 5-11, 34, 39 and 40 remain in this application.

Claim 40 is new and finds basis in original claim 12.

Claims 1, 5-11, 34 and 39 stand rejected under 35 USC § 103 as being unpatentable over Higgins III (U.S. Patent No. 6,147,236) and Higashidate *et al.* (Journal of Chromatography (1990) 515:295-303). Claims 1, 5-11, 34 and 39 further stand rejected under 35 USC § 103 as being unpatentable over the combined teachings of Mitchell (U.S. Patent No. 4,588,717), Mishkel *et al.* (Bailliere's Clinical Haematology, Vol. 3, No. 3, July 1990, pp. 625-649) and Kamarei *et al.* (U.S. Patent No. 4,879,312).

Before addressing these rejections, it is worthwhile to review the invention briefly.

Summary of Invention

The invention provides nutritional supplements comprising sterol esters of omega-3 fatty acids that lower serum cholesterol and triglygeride levels

The instant invention concerns Applicant's surprising discovery that a sterol ester of an omega-3 fatty acid is useful for reducing the level of serum cholesterol and serum triglycerides in mammals, particularly humans (specification, page 3, lines 5-10). In a particularly preferred embodiment, the invention provides a nutritional supplement for lowering cholesterol and triglyceride levels in the blood stream of a subject, said nutritional supplement comprising: a sterol ester of an omega-3 fatty acid, wherein said omega-3 fatty acid is selected from the group consisting of eicosapentaenoic acid 20:5ω3 (EPA), docosahexaenoic acid 22:6ω3 (DHA) and stearidonic acid 18:4ω3 (SA), as recited in current claim 1.

Ester linkage of the sterol to the omega-3 fatty acid has many advantages

It is advantageous for appearance, palatability etc. of the nutritional supplements of the invention that the sterol and the omega-3 fatty acid are chemically joined through an ester linkage. Free sterols are not very soluble in lipids and this complicates their use in lipid-based

foods (see the specification at page 3 lines 29-30). Hence, it is advantageous that the sterol is esterified to the omega-3 fatty acid (see the specification at page 4 lines 5-10). This issue is discussed in greater detail in the Declaration of H. Stephen Ewart, Ph.D. under 37 CFR 1.132 dated July 10, 2002 and submitted to the Patent Office with Applicant's submissions of July 15, 2002. In his Declaration, Dr. Ewart explains that a mere combination or mixture of a sterol and an omega-3 fatty acid results in a pasty, grainy composition. This is undesirable for use as a nutritional supplement in the form of either a food additive or a pharmaceutical composition, where appearance, palatability and processing characteristics are important. It was necessary to esterify the sterol to the omega-3 fatty acid to obtain a transparent, homogeneous oily liquid having properties useful as a nutritional supplement.

Therefore, esterification of the sterol to the omega-3 fatty acid is advantageous. But, for the reasons discussed herein, prior to the invention, it would not have been expected that a sterol ester of an omega-3 fatty acid would be effective to reduce both serum cholesterol and triglyceride levels.

Sterols, particularly phytosterols, reduce cholesterol, and are poorly absorbed by the intestinal tract

One approach for reducing serum cholesterol levels is to interfere with intestinal absorption of cholesterol. Certain phytosterols (plant sterols) such as stigmasterol and β-sitosterol lower serum cholesterol levels by inhibiting absorption of both dietary and biliary cholesterol from the small intestine (see specification, paragraph bridging pages 1 and 2). It has also been suggested that a sterol esterified with a fatty acid may be more effective for reducing serum cholesterol. In any event, the mechanism by which phytosterols or phytosterol esters inhibit absorption of dietary cholesterol by the digestive tract is not fully understood but may involve competitive inhibition of cholesterol uptake from the intestinal lumen or inhibition of cholesterol esterification in the intestinal mucosa. It is known that phytosterols themselves are only poorly absorbed (see the specification at page 7 lines 25-30). See also e.g. Nguyen, T.T. (1999) The cholesterol-lowering action of plant stanol esters. J. Nutr. 129: 2109-2112 (copy enclosed). Moreover, phytosterol esters too may be poorly absorbed by the intestinal tract (see the specification at page 2 lines 6-30).

Omega-3 fatty acids are absorbed into the bloodstream, reduce triglyceride levels but increase cholesterol levels

Fish oils are rich in omega-3 fatty acids, particularly EPA, DHA, and also contain substantial amounts of SA (see the specification at page 6 line 8 through page 7 line 5). It is known that omega-3 fatty acids lower plasma triglyceride levels principally by inhibiting synthesis of triacylglycerol and very low density lipoproteins in the liver (see the specification at page 7 lines 6-9). In contrast, in order to effect a reduction in blood stream triglyceride levels, omega-3 fatty acids must be absorbed from the intestinal lumen into the blood stream. Fish oil omega-3 fatty acids must travel in the bloodstream to the liver where they modulate the activity of several enzymes of carbohydrate and lipid synthesis. The overall effect is the promotion of hepatic fatty acid oxidation and reduction of triacylglycerol synthesis, with a consequent reduction of triacylglycerol release into the circulation. See e.g. the Connor & Connor reference cited in the instant specification at page 7 lines 9-11.

Although omega-3 fatty acids are known to lower triglyceride levels, the preponderance of scientific evidence is that omega-3 fatty acids do not lower cholesterol, and may actually increase it. Harris (1989) J. Lipid. Res. 30:785-807, discussed in the present patent application at page 7, lines 25-27, concluded that fish oil consumption (omega-3 fatty acids) results either in no change in serum cholesterol, or actually leads to an increase in LDL cholesterol. Similarly, a recently reported study found that EPA and DHA, the principal omega-3 fatty acids found in fish oil, increased LDL cholesterol levels. See Stalenhoef *et al.* (2000) The effect of concentrated N-3 fatty acids versus gemfibrozill on plasma lipoproteins, low density lipoprotein heterogeneity and oxidizability in patients with hypertriglyceridemia. Atherosclerosis 153:129-138 (copy enclosed).

Hence, at the time of the invention, it was unknown whether these opposing requirements would be met. In particular, prior to the invention, it was not known or predictable whether the sterol component of the ester would prevent the fatty acid from being absorbed in the bloodstream. Although there are digestive enzymes in the intestinal lumen with esterase activity that might free the fatty acid from its ester linkage with the sterol, the degree to which this would occur was unpredictable and therefore it was unclear whether a sufficient amount of the omega-3

fatty acid would be released to have a significant effect on serum triglyceride levels. See the Declaration of H. Stephen Ewart, Ph.D. dated July 10, 2002 and filed with Applicant's response of July 15, 2002.

LDL cholesterol is the form of blood cholesterol lowered by ingestion of sterols. Thus, irrespective of the above-described complications arising from the esterification of sterols with the omega-3 fatty acids, based on the totality of the available scientific literature, it would have been expected that the cholesterol-*increasing* effect of the omega-3 fatty acid might reduce or counteract the cholesterol-lowering effect of the sterol. It would not have been expected that the combination of the sterol and the omega-3 fatty acid, particularly in esterified form, would result in a reduction in both cholesterol and triglyceride levels, as disclosed in the present application (see the 1.132 Declaration of H. Stephen Ewart, Ph.D. dated July 10, 2002).

Nevertheless, as shown in the Declaration of H. Stephen Ewart dated March 27, 2001 and submitted with Applicant's paper of April 12, 2001, surprisingly, the compositions of the invention do indeed lower both serum triglyceride and cholesterol levels, as claimed.

Issues

Claims 1, 5-11, 34 and 39 stand rejected under 35 USC § 103 as being unpatentable over Higgins III (U.S. Patent No. 6,147,236) and Higashidate *et al.* (Journal of Chromatography (1990) 515:295-303). This rejection was made in the Office Action of November 26, 2002.

Higgins III is only potentially citable as a reference under 35 USC § 102(e). With Applicant's response of April 18, 2003, Applicant filed a Declaration under 37 CFR § 1.131 by the inventor Jeffrey L. C. Wright establishing a date of invention prior to December 15, 1998, the filing date of Higgins III. In the Final Office Action of July 16, 2003, the Examiner maintained the rejection on the basis that Applicant's 1.131 Declaration was insufficient to prove a date of invention before the filing date of Higgins III. Applicant traverses this rejection and submits that Higgins III is not prior art under 35 USC § 102(e) and the rejection over Higgins III must therefore be withdrawn.

Claims 1, 5-11, 34 and 39 further stand rejected under 35 USC § 103 as being

unpatentable over the combined teachings of Mitchell (U.S. Patent No. 4,588,717), Mishkel *et al.* (Bailliere's Clinical Haematology, Vol. 3, No. 3, July 1990, pp. 625-649) and Kamarei *et al.* (U.S. Patent No. 4,879,312). Applicant traverses this rejection and submits that the instant claims patentably distinguish from the cited references or any combination thereof.

Argument

Concerning 35 USC § 103

Higgins III and Higashidate *et al.*

Claims 1, 5-11, 34 and 39 stand rejected under 35 USC § 103 as being unpatentable over Higgins III (U.S. Patent No. 6,147,236) and Higashidate *et al.* (Journal of Chromatography, (1990) 515:295-303).

Applicant traverses this rejection.

Higgins III is not prior art

As stated in Applicant's response of April 18, 2003, the instant application was filed on August 30, 1999. Higgins III was filed on December 15, 1998 and issued on November 14, 2000. Therefore, Higgins III is only potentially citable as a reference under 35 USC § 102(e). With Applicant's response of April 18, 2003 Applicant filed a Declaration under 37 CFR § 1.131 by the inventor Jeffrey L. C. Wright establishing a date of invention prior to December 15, 1998, the filing date of Higgins III. Higgins III therefore is not prior art and cannot be cited under 35 USC 103.

Higashidate *et al.* does not cure the defects in Higgins III

The second cited reference, Higashidate *et al.*, does not by itself render obvious the instant claims. Higashidate *et al.* were concerned with methods for extracting methyl esters of DHA and EPA from fish oil. Methyl esters of DHA and EPA were extracted by supercritical fluid extraction with carbon dioxide and directly introduced into a silica gel column coated with silver nitrate. Supercritical fluid chromatography with carbon dioxide was then performed by

stepwise changes of the pressure at the column outlet. The EPA and DHA methyl esters thus separated were fractionated by reducing the pressure of column effluent to atmospheric. This process enriched EPA and DHA methyl esters from 12% to 93% and from 13% to 82% respectively. See the abstract of the reference.

Higashidate *et al.* were concerned only with improving chromatographic techniques for fractionating methyl esters of DHA and EPA. The reference is not concerned with the pharmacological activity of omega-3 fatty acids, and mentions merely by way of background that fish oil is a rich source of fatty acids such as EPA and DHA, which is well known. See Higashidate *et al.* at page 295, first paragraph. The reference contributes nothing new to the body of literature concerning omega-3 fatty acids. Indeed, at page 302, the authors acknowledge that information about DHA and EPA was provided by an employee of Jasco, the supplier of the chromatography equipment. Clearly, the focus of the reference is on chromatography techniques, not the pharmacological properties of DHA and EPA.

Critically, Higashidate *et al.* do not disclose or suggest sterol esters of DHA, EPA and SA, and their use for reducing cholesterol and triglyceride levels as instantly claimed.

The Examiner's argument concerning Higgins III

The Examiner has rejected Applicant's arguments, stating in the Final Office Action of July 16, 2003 that:

> The declaration filed on 5/5/03 under 37 CFR 1.131 has been considered but is ineffective to overcome the cited reference. The arguments that Higgins III (US Patent 6,147,236) was filed on 12/15/1998 and issued on 11/14/2000 and the date of the present invention is prior to 12/15/1998 because of a communication of the inventor to the Attorney. It is unclear what invention was under consideration at that time. There is no proof that the claimed invention was conceived before 12/15/1998 by seeing the copy of the letter. Probably the conception of invention of Higgins III may be prior to 12/15/1998 as this is the filing date.
>
> Even if there would have been a proof, when claims will be considered allowable than the Board of Interference will decide the issue of priority.

Applicant's Declaration under 37 CFR §1.131 antedates Higgins III

Applicant disagrees and submits that the Declaration of Jeffrey L. C. Wright pursuant to 37 CFR § 1.131 is sufficient to antedate the Higgins III reference.

The Examiner contends that the invention claimed in the Higgins III reference was likely conceived before December 15, 1998 (i.e. the filing date of the reference). The Examiner concludes that even if she had been satisfied that Applicant had sworn behind the Higgins III reference, the issue of priority will be determined by the Board of Interferences.

Applicant submits that, because Higgins III does not claim the subject matter of any of instant claims 1, 5-11, 34 or 39, priority of invention is not at issue. Hence, the date on which the invention claimed in the Higgins III reference is not relevant. The Higgins III reference is only potentially citable as prior art under 35 USC 102(e) and to remove this reference, Applicant need only establish a date of invention prior to the effective U.S. filing date of the Higgins III reference. Applicant submits that, in accordance with 35 USC § 104 and 37 CFR § 1.131, the Declaration of Jeffrey L. C. Wright establishes that prior to the filing date of the Higgins III reference (i.e. prior to December 15, 1998) Applicant made the instantly claimed invention in a NAFTA country.

The Examiner contends that it is unclear from Applicant's 1.131 Declaration what invention was under consideration prior to December 15, 1998 and that there is no proof that the invention was conceived before December 15, 1998.

Applicant disagrees. Exhibit A to the Declaration under 37 CFR § 1.131 of the inventor Jeffrey L. C. Wright is a redacted copy of a letter from Dr. Wright to his original patent agents explaining his conception of the instantly claimed invention. Specifically, in his letter, dated before December 15, 1998, Dr. Wright stated:

> In this case we wish to patent a bifunctional nutraceutical that will simultaneously lower serum triglycerides and cholesterol levels - two key risk factors of cardiovascular disease....Our proposal then is to esterify fish oil omega 3 fatty acids (different in structure from the omega 6 canola oils and markedly different in biological properties) with natural sterols...thus creating our bifunctional

> nutraceutical product which will lower cholesterol and triglycerides. That is the crux of our patent. (emphasis added)

Applicant submits that there is no doubt as to the invention contemplated in Dr. Wright's statement above. Dr. Wright clearly contemplated that a sterol ester of an omega-3 fatty acid derived from fish oil would produce a nutritional supplement for simultaneously lowering serum triglyceride and cholesterol levels. This is the invention defined in instant claim 1. The specification makes clear that a wide range of sterols may be used, particularly phytosterols (i.e. "natural" sterols as described above by Dr. Wright). See the instant specification at page 4 line 30, through page 6 line 7.

In the above-mentioned letter, Dr. Wright speaks of omega-3 fatty acids from fish oil. Instant claim 1 specifies that the omega-3 fatty acid is SA, EPA or DHA. As discussed in the specification at the paragraph bridging pages 6 and 7, EPA and DHA are the predominant omega-3 fatty acids found in fish oil, and SA is also commonly found in fish oil. Accordingly, Dr. Wright's reference to omega-3 fatty acids from fish oils refers to a known and discrete class of omega-3 fatty acids as instantly claimed. Dr. Wright makes clear reference to the formation of an ester of the natural sterol and the fish oil omega-3 fatty acid and specifically that the resulting bifunctional composition would be useful as a "nutraceutical" (i.e. a nutritional supplement), useful for reducing both serum cholesterol and serum triglycerides, as instantly claimed. Hence, Applicant submits that the Declaration of Dr. Wright under 37 CFR § 1.131 is unmistakably directed to the instantly claimed invention and establishes that the claimed invention was made prior to December 15, 1998.

As discussed above, in the absence of the Higgins III reference, the Higashidate *et al.* reference does not by itself render obvious the instant claims.

Reconsideration and withdrawal of the rejections of the claims over Higgins III and Higashidate *et al.* are therefore requested.

Mitchell, Mishkel *et al.* and Kamarei *et al.*

In the Final Office Action, the Examiner maintains the rejection of the claims under 35 USC § 103 as being unpatentable over the combined teachings of Mitchell, Mishkel *et al.* and

Kamarei *et al.* At page 2 of the Office Action, the Examiner states that:

> Applicant's arguments filed on 5/5/03 have been fully considered but were not persuasive. Examiner's rejection is based on only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).
>
> Note, that the rejection is over combined teaching of the cited references. Therefore, argument of teaching of single reference is not considered a proper response. Examiner notes, that Applicants discuss references separately.

Applicant understands the Examiner's above comments to relate to Applicant's previous arguments concerning the Mitchell, Mishkel *et al.* and Kamarei *et al.* references. In the Final Action, the Examiner then depicts at pages 3-5 various chemical structures. Applicant notes that these structures are taken from the Higgins III patent, and not from any of Mitchell, Mishkel *et al.* or Kamarei *et al.*, the references cited in this further §103 rejection. As discussed above, the Higgins III patent is not prior art and the structures depicted at pages 3-5 of the Office Action must therefore be disregarded.

Applicant traverses this rejection and maintains that the instant claims patentably distinguish from Mitchell, Mishkel *et al.* and Kamarei *et al.*, or any combination thereof.

Previous §103 rejections over Mitchell and Kamarei *et al.* have been overcome

Applicant first notes that § 103 rejections over the Mitchell and Kamarei *et al.* references have been previously overcome during the prosecution of this application. The Mitchell reference was first cited in the Office Action of July 3, 2001 and the rejection maintained in a Final Office Action of December 17, 2001.

However, in view of Applicant's amendment and arguments of April 15, 2002, the rejections over Mitchell were withdrawn in the subsequent non-final Office Action of April 26, 2002.

Similarly, the Kamarei reference was first cited in a § 103 rejection in the non-final Office Action of April 26, 2002. This rejection was withdrawn in the Office Action of

November 26, 2002, in response to Applicant's arguments submitted with a Request for Continued Examination on July 15, 2002.

Hence, both the Mitchell and Kamarei *et al.* references have been dealt with extensively during the prosecution of this application, and rejections over each of these references have already been withdrawn.

The Mitchell reference

The Examiner argues that Mitchell teaches vitamin supplements containing phytosterol esters of polyunsaturated fatty acids (PUFAs).

Applicant notes that Mitchell concerns vitamin supplements of three types: (a) steroid vitamin supplements; (b) mineral vitamin supplements; and (c) diet pills and preparations. Only the disclosure of steroid vitamin supplements is relevant to the Examiner's objection.

At column 1 line 15 through column 2 line 10, Mitchell states that direct introduction of steroids and hormones into the digestive tract and/or bloodstream can result in undesirable side effects such as acne, voice changes, menstrual irregularities, post-menopausal bleeding, swelling of the breasts, etc. Moreover, there is poor absorption of orally ingested steroids and hormones into the human digestive tract and also many steroids and hormones are converted into toxic substances in the digestive tract. Hence, Mitchell contends that there is a need for chemical formulations and methods for administering steroids and hormones to humans and other animals without directly introducing the hormones and steroids into the bloodstream or digestive tract.

The solution proposed by Mitchell is a vitamin supplement comprising a phytosterol ester, such as fatty acid esters of phytosterol, stigmasterol or taraxasterol. In preferred embodiments, the fatty acids linoleic acid, linolenic acid and arachidonic acid are used to form the phytosterol ester. See Mitchell column 3 lines 20-36.

Mitchell states that, in the phytosterol ester vitamin supplements of his invention, steroids and hormones are produced after the vitamin supplements reach the cells of the animal or plant. Hence the phytosterol ester vitamin supplements are introduced into the animal or plant as

relatively non-toxic phytosterol esters which are then converted to steroids and hormones only after reaching the cells, thereby minimizing the adverse side-effects of steroids and hormones experienced in the prior art when the steroids and hormones are introduced directly into the digestive tract and bloodstream (see Mitchell at column 3 lines 37-48). Mitchell further states that the fatty acid portion of the ester serves to enhance the absorption of the phytosterols into the cells of the animal or plant (see Mitchell at column 3 lines 55-58).

All of Examples 1-75 of Mitchell, concerning phytosterol ester vitamin supplements, involved the use of linoleic acid, linolenic acid or arachidonic acid as the fatty acid. Mitchell does not disclose the fish oil omega-3 fatty acids DHA, EPA and SA, useful for lowering triglyceride levels, as instantly claimed.

Mitchell is not concerned with reducing either serum cholesterol levels or serum triglyceride levels and makes no mention of these matters. There is no discussion in Mitchell of the utility of phytosterols for reducing cholesterol levels. Similarly, Mitchell does not discuss the triglyceride lowering effects of omega-3 fatty acids, particularly omega-3 fatty acids from fish oils, such as EPA, DHA and SA. Mitchell concerns the use of phytosterol esters of fatty acids for an entirely different purpose than the compositions of the instant invention. In Mitchell, the fatty acid is present only for the stated purpose of enhancing absorption of the phytosterol. Mitchell does not recognize or identify any differences between omega-3 fatty acids and other fatty acids, or the value of fish oil omega-3 fatty acids, particularly DHA, EPA and SA for reducing triglyceride levels. Notably, Mitchell generally teaches away from the use of omega-3 fatty acids, stating at column 5, lines 60-65 that the most preferable fatty acid for use in his invention is linoleic acid (i.e. not an omega-3 fatty acid) primarily because linoleic acid is inexpensive and stable.

Moreover, Mitchell is non-enabling. At column 8, lines 18-33, Mitchell states that phytosterol esters can be formed simply by mixing the phytosterol and the fatty acid in bringing the mixture to a temperature of 15-45°C at atmospheric pressure for about 1-3 hours. These are the conditions used in Mitchell's working examples. But mixing a phytosterol and fatty acid at room temperature clearly will not result in an esterification reaction. Attached is a Declaration under 37 CFR §1.132 by Jaroslav Kralovec Ph.D., a chemist employed by the assignee Ocean

Nutrition Canada Limited. As discussed in his Declaration, Dr. Kralovec mixed a phytosterol and a fatty acid at room temperature and pressure as taught in Mitchell's examples. As expected, thin layer chromatography analysis determined that no ester formation occurred. Mitchell does not describe how he tested for or detected ester formation, and it appears unlikely that Mitchell could have made esters under the conditions he describes. The reaction conditions taught by Mitchell do not work, and these are the only reaction conditions Mitchell provides. The skilled person could not produce esters following the teachings of Mitchell and Mitchell is therefore not enabling prior art.

Mishkel *et al.*

The Examiner contends that Mishkel *et al.* teach that omega-3 fatty acids lower cholesterol and have a beneficial effect on preventing and treating cardiovascular disease.

Applicant disagrees. Mishkel *et al.* is a general review article that, contrary to the Examiner's assertion, makes no specific mention of omega-3 fatty acids having a cholesterol lowering effect. Whatever Mishkel *et al.* discloses concerning the potential health benefits of omega-3 fatty acids, it is clear that reducing cholesterol levels is not one of them. Mishkel *et al.* do not cite any studies showing that omega-3 fatty acids reduce cholesterol and indeed cites a number of studies showing that consumption of omega-3 fatty acids either has no beneficial effect on cholesterol levels or even increases cholesterol levels.

In this regard, at page 629, Mishkel *et al.* cite the work Weiner *et al.* (1986) who found that consumption of cod liver oil (containing the omega-3 fatty acid EPA) resulted in an increase in total plasma cholesterol.

Also at page 629, Mishkel *et al.* discuss the work of Shimokawa and Vanhoutte (1988) who found that antiatherosclerotic benefit of cod liver oil was independent of any favourable changes in cholesterol.

Similarly, at page 631, Mishkel *et al.* discuss the work of Davis *et al.* (1987) who reported that cholesterol levels remained quite elevated in Rhesus monkeys consuming omega-3 fatty acids.

At page 632, Mishkel *et al.* report that fish oils modestly elevate HDL cholesterol, citing Holub *et al.* (1987), and also that Harris *et al.* (1988) reported that although administration of omega-3 fatty acids indeed lowers triglyceride levels in hyperlipoproteinaemic patients, LDL cholesterol levels were raised in patients with previously high or normal levels. Mishkel *et al.* also conclude in the same passage that it is probable that earlier studies demonstrating a lowering of LDL cholesterol were a result of a combination of reduced saturated fat intake and a large increase in the intake of polyunsaturated fats (i.e. due to a favourable change in the saturated to unsaturated fat ratio and not as a result of the consumption of omega-3 fatty acids *per se*).

Similarly, at page 636, Mishkel *et al.* discuss the work of Burr *et al.* (1989) who reported that the consumption of small amounts of fish was not associated with favourable changes in cholesterol status.

Thus, on the whole, Mishkel *et al.* do not teach or suggest that omega-3 fatty acids are useful for lowering cholesterol levels and indeed cite many reports indicating that omega-3 fatty acids have either no effect on cholesterol or increased cholesterol levels.

This is consistent with Applicant's submissions of July 15, 2002 wherein Applicant discussed the findings of Stalenhoef *et al.* (2000) that EPA and DHA actually increase LDL cholesterol levels. See paragraph 12 of the 37 CFR § 1.132 Declaration of H. Stephen Ewart dated July 10, 2002.

Applicant therefore maintains that Mishkel *et al.* neither teach or suggest that omega-3 fatty acids lower serum cholesterol levels. Moreover, Mishkel *et al.* make no mention of sterol esters of omega-3 fatty acids as instantly claimed.

Kamarei *et al.*

The Examiner contends that the Kamarei *et al.* patent teaches that a diet rich in omega-3 fatty acids has beneficial effects in humans, including a reduction in plasma cholesterol and triglyceride levels, improved fat tolerance, etc. The Examiner also states that Kamarei *et al.* teach that one of EPA and DHA reduces triglyceride and very low-density lipoprotein (VLDL) serum levels and reduces whole blood viscosity.

Applicant disagrees. Applicant first notes that Kamarei *et al.* were concerned only with use of omega-3 fatty acids for causing or increasing angiogenesis i.e. formation of new blood vessels. Kamarei *et al.* were not concerned with reducing triglyceride levels or cholesterol levels, as instantly claimed.

As noted by the Examiner, Kamarei *et al.* do state at column 2 lines 39-43 that there is much evidence that a diet rich in omega-3 fatty acids has beneficial effects in humans, including a reduction in plasma cholesterol and triglyceride levels, improved fat tolerance, prolonged bleeding time, reduced platelet counts and decreased platelet adhesiveness, citing Lee *et al.* (1985) New England Journal of Medicine 312:1217 and Phillipson *et al.* (1985) New England Journal of Medicine 312:1210. However, these are merely passing statements in the background of the invention section of Kamarei *et al.* and are not concerned with Kamarei *et al.'s* invention concerning angiogenesis.

Moreover, as discussed above, the preponderance of scientific evidence to date suggests that omega-3 fatty acids do not reduce cholesterol levels but may rather increase cholesterol levels. This point was discussed in detail in Applicant's submissions of July 15, 2002, in particular in Applicant's discussion of Stalenhoef *et al.* (2000) as discussed above.

More importantly, as Applicant discussed in Applicant's submissions of July 15, 2002, Kamarei *et al.* make no mention whatsoever of phytosterols, or esters of sterols and omega-3 fatty acids as instantly claimed.

Improper citation of Higgins III

It is important to note that the §103 rejection over Mitchell, Mishkel *et al.* and Kamarei *et al.* in the Office Action of November 26, 2002, maintained in the Final Office Action, contains an improper reference to the Higgins III patent. At page 5, third paragraph of the Office Action of November 26, 2002, in concluding the obviousness rejection over Mitchell, Mishkel *et al.* and Kamarei *et al.*, the Examiner states that:

> It would have been obvious to one skilled in the art to prepare additional beneficial nutritional supplement[s] using sterols with a pendent ester functionality which when hydrolyzed provides another cholesterol-lowering agent. (emphasis in original)

This statement is nearly a direct quote from Higgins III at column 4, lines 11-14. Hence, this statement erroneously appears without attribution in a rejection based on the Mitchell, Mishkel *et al.* and Kamarei *et al.* references. More importantly, as discussed above, Higgins III is not prior art, and must be disregarded.

Similarly, as discussed above, at pages 3 to 5 of the Final Action of July 16, 2003, in what Applicant understands to be the Examiner's response to Applicant's arguments concerning the §103 rejection over Mitchell, Mishkel *et al.* and Kamarei *et al.*, various chemical structures are depicted without explanation. Applicant notes that these structures are taken from the Higgins III patent, and not from any of Mitchell, Mishkel *et al.* or Kamarei *et al.* As discussed above, the Higgins III patent is not prior art and the structures depicted at pages 3-5 of the Office Action must therefore be disregarded.

Applicant's submissions concerning the combined teachings of Mitchell, Mishkel *et al.* and Kamarei *et al.*

The Examiner's reasons for the rejection over Mitchell, Mishkel *et al.* and Kamarei *et al.* in the final Office Action of July 16, 2003 are set forth at pages 2 through 5 of the Office Action. As discussed above, the chemical drawings shown at pages 3 through 5 are taken from the Higgins III reference, which is not prior art. What is new in the Final Action is the Examiner's statement at page 5 that she disagrees with Applicant's argument that Mishkel *et al.* do not teach that omega-3 fatty acids lower cholesterol. In particular, she mentions Singer *et al.* (1987) as being cited by Mishkel *et al.* where EPA was used for patients having mild hypertension and a decline in blood pressure was observed. It appears that otherwise, the Examiner relies on the arguments raised in the Office Action of November 26, 2002.

Addressing first the Examiner's further arguments concerning Mishkel *et al.*, Applicant acknowledges that Mishkel *et al.* report many studies in which health benefits of diets including fish oils containing omega-3 fatty acids such as EPA and DHA were observed. Indeed, the

beneficial properties of EPA and DHA for reducing triglyceride levels are known. But, as discussed above, the Mishkel *et al.* reference itself, and the papers discussed therein conclude that EPA and DHA however do not have any beneficial effect on serum cholesterol levels and even increase them. This is critical to the application of Mishkel *et al.* in a rejection of the instant claims, which recite lowering both triglyceride and serum cholesterol levels.

Specifically addressing the Examiner's remarks concerning Singer *et al.* (1997) referenced in Mishkel *et al.*, Singer *et al.* report on the long term effects of a mackerel diet. Twelve mildly hypertensive male patients ate two cans of mackerel /day for two weeks and then three cans/week for eight months. Caloric intake was balanced primarily by removal of "cold cuts" from the diet. A drop in blood pressure, blood triacylglycerols, and total and LDL-cholesterol were observed after the first two weeks. Blood pressure, total and LDL-cholesterol were still reduced at two months relative to the control group. By eight months only blood pressure remained slightly decreased. This was a small study, and not placebo controlled. It involved addition of fish to the diet, not just EPA, DHA and/or SA as in the instant claims. Clearly, constituents of canned mackerel other than EPA, DHA and SA may affect cholesterol levels. Also, as discussed herein, the results observed may also be a function of increasing the unsaturated:saturated fat ratio. There is no clear teaching in Singer *et al.* that EPA, DHA and SA reduce cholesterol levels.

The full text of the Examiner's rejections over the Mishkel *et al.*, Mitchell and Kamarei *et al.* references is set forth in the non-final Office Action of November 26, 2002 at pages 3-5:

> Instant claims differ from the reference in claiming nutritional supplement of phytosterol ester with specific fatty acids i.e. docosahexaenoic acid, stearidonic acid and eicosahexaenoic acid where US '717 teaches phytosterol ester with fatty acids especially containing poly unsaturated fatty acid approximately 2-22 carbon atoms. See examples 51-75 in col. 6, equation 2 in cols 15, 16, 17 and 18. Mishkel et al. teaches that polyunsaturated fatty acids from fish oil is used to preventing and treating cardiovascular disease. Furthermore, it teaches two major biologically active fish oil compounds, EPA and DHA.

> Note, that Kamarie that n-3 PUFA i.e. eicosapentaenoic acid (EPA) and DHA reduces triglyceride and very low-density lipoprotein (VLDL) serum levels and reduces whole blood viscosity. (See lines 39-59, col. 2; lines 13-54, col. 3 and Table 1 and 2 in col. 4).
>
> It would have been obvious to one skilled in the art to prepare additional beneficial nutritional supplement using sterols with a pendent ester functionality which when hydrolyzed provides another cholesterol-lowering agent. Since Mishkel teaches that fish oil contains omega-3 fatty acids (a class of PUFA) which includes docosahexaenoic acid (DHA) and eicosahexaenoic acid (EPA), see especially last para on page 625 of Mishkel reference). There has been ample motivation provided by the prior art to prepare the instant invention.

Again, it must be noted that the first sentence in the last paragraph quoted above is taken from the Higgins III reference (which is not prior art), and not from any of Mitchell, Mishkel *et al.* or Kamarei *et al.*

In the passage quoted above, the Examiner contends that:

(1) Mitchell teaches phytosterol esters with fatty acids, particularly polyunsaturated fatty acids approximately 2-22 carbon atoms in length;

(2) Mishkel *et al.* teach that polyunsaturated fatty acids from fish oil are used to prevent and treat cardiovascular disease and that EPA and DHA are biologically active fish oil compounds; and

(3) Kamarei *et al.* teach that EPA and DHA reduce triglyceride and very low density lipoprotein serum level.

Applicant traverses this rejection and submits that it would not have been obvious to modify the teachings of Mitchell as proposed by the Examiner.

As discussed above, Mitchell is ostensibly concerned with delivering steroids and hormones without adverse side effects. Mitchell is not concerned with reducing either serum triglyceride or cholesterol levels and makes no mention of the benefits of phytosterols for reducing cholesterol levels or of omega-3 fatty acids, particularly EPA, DHA and SA, for reducing serum triglyceride levels. In fact, Mitchell's preferred fatty acid is linoleic acid, which is not an omega-3 fatty acid, recommended by Mitchell as being both inexpensive and stable (see

Mitchell at column 5 lines 60-65). Given the enormous body of literature concerning cardiovascular disease and the role of sterols and omega-3 fatty acids in affecting cholesterol and triglyceride levels, the skilled person would not look to Mitchell as the source of an answer to the problem of reducing both serum triglyceride and cholesterol levels. The Mitchell reference is not in the field of Applicant's invention nor is the Mitchell reference in any way pertinent to the problem with which the invention is concerned. Mitchell is simply non-analogous art. "In order to rely on a reference as a basis for rejection of an applicant's invention, the reference must either be in the field of Applicant's endeavour or, if not, then be reasonably pertinent to the particular problem with which the inventor was concerned." *In re Oetiker*, 24 USPQ 2d 1443 (Fed. Cir. 1992).

Even if one were to look to Mitchell as a source of a solution to the problem of reducing both serum triglyceride and cholesterol levels, the skilled person would not then look to Kamarei *et al.* to modify the teachings of Mitchell to substitute DHA, EPA or SA as the fatty acid moiety in the sterol ester. Like Mitchell, Kamarei *et al.* is not relevant to Applicant's field of endeavour. As discussed above, Kamarei *et al.* were concerned with the use of omega-3 fatty acids solely for provoking or enhancing angiogenesis, and not with reducing serum triglyceride and cholesterol levels, as instantly claimed.

Merely by way of background do Kamarei *et al.* state that a diet rich in omega-3 fatty acids has beneficial effect in humans, including a reduction in plasma cholesterol and triglyceride levels, improve fat tolerance, prolonged bleeding time, etc. But as discussed above, Kamarei *et al.* do not specifically ascribe the reduction in cholesterol levels to omega-3 fatty acids. Importantly, as discussed in detail above above, the prevailing view, both at the time of the invention and today is that omega-3 fatty acids do <u>not</u> lower cholesterol levels and indeed <u>increase</u> them.

Kamarei *et al.* make no mention of sterols, such as phytosterols, their utility for reducing cholesterol levels, or phytosterol esters. This stands to reason, as Kamarei *et al.* were not concerned with reducing either serum triglyceride or cholesterol levels.

Thus, Kamarei *et al.*, describe the use of omega-3 fatty acids for increasing angiogenesis,

a problem and field of endeavour unrelated to the problem solved by Applicant's invention. Hence Kamarei *et al.*, like Mitchell, concerns a non-analogous art. The Examiner cites Kamarei *et al.* only for its disclosure that omega-3 fatty acids lower triglyceride and cholesterol levels. One would not look to such non-analogous prior art for this teaching. Moreover, the beneficial effects of omega-3 fatty acids on triglyceride levels are known and the skilled person would not look to art relating to angiogenesis for this teaching. Kamarei *et al.*'s passing reference to diets containing omega-3 fatty acids as lowering cholesterol levels would not lead the skilled person to believe that omega-3 fatty acids themselves, particularly EPA, DHA and SA, reduce cholesterol levels, in view of the large body of literature to the contrary.

Neither Mitchell nor Kamarei *et al.* are analogous prior art, and therefore do not form the proper basis for a rejection under 35 USC § 103. *In re Oetiker*, supra. Moreover, as neither reference is concerned with the problem of lowering either serum triglyceride or cholesterol levels using sterols and/or omega-3 fatty acids, there is no motivation to combine the references. The mere fact that the references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 16 USPQ 2d 1430 (Fed. Cir. 1990).

Only Mishkel *et al.*, a review article concerning the cardiovascular effects of omega-3 fatty acids, is relevant to Applicant's field of endeavour. Mishkel *et al.* are not concerned with sterol esters of omega-3 fatty acids, and the Examiner relies on Mishkel *et al.* only for the teaching that omega-3 fatty acids from fish oils lower cholesterol levels. But as discussed above, contrary to the Examiner's assertions, Applicant has not found a single specific statement in Mishkel *et al.* that omega-3 fatty acids from fish oils reduce serum cholesterol levels and indeed, as discussed above, Mishkel *et al.* cite numerous references which found that omega-3 fatty acids from fish oils actually increase serum cholesterol levels. Thus, on the balance, and in accordance with current scientific understanding, Mishkel *et al.* in fact teach that omega-3 fatty acids from fish oil either do not reduce serum cholesterol levels or actually increase them. Applicant emphasizes that a reference must be considered in its entirety, i.e. as a whole, including portions that would lead away from the claimed invention. *W. L. Gore and Associates, Inc. v. Garlock, Inc.* 220 USPQ 303 (Fed. Cir. 1993).

Hence, Applicant submits that this rejection is based on two non-analogous references that are not in any way concerned with compositions that reduce serum cholesterol and/or triglyceride levels, and a third reference that on the whole, teaches away from Applicant's invention. The necessary motivation to combine the references is missing. At page 2 of the Final Office Action, the Examiner states that the rejection is based only on knowledge which was within the level of ordinary skill in the art at the time the invention was made and does not include knowledge gleamed only from the Applicant's disclosure. Applicant notes that, nevertheless, the level of skill in the art cannot itself be relied upon to provide the suggestion to combine references. *Al-Site Corp. v. VSI International Inc.* 50 USPQ 2d 1161 (Fed. Cir. 1999). In the instant case, there is nothing in the references that suggests that they should be combined. It is only with impermissible hindsight of Applicant's invention that any connection between these three references can be made.

Secondly, even if the missing motivation to combine the references were present, the skilled person would not have had a reasonable expectation of success that a sterol ester of EPA or DHA would be useful for reducing both serum triglyceride and cholesterol levels. As discussed above, and as discussed in the Declaration of H. Stephen Ewart, Ph.D. dated July 10, 2002, prior to the instant application, a skilled person would not have predicted that with any reasonable expectation of success that: (1) the cholesterol increasing effect of the DHA or EPA would not negate the cholesterol-lowering effect of the sterol; and (2) that a sufficient amount of the omega-3 fatty acid would be released from the sterol ester so as to permit absorption of the omega-3 fatty acid into the bloodstream where it would be effective to lower triglyceride levels. Indeed, the Mishkel *et al.* reference, citing numerous reports of the cholesterol-increasing effects of omega-3 fatty acids, specifically teaches away from any expectation of success whatsoever.

Further, Applicant submits that even if one were to modify the teachings of Mitchell by substituting the EPA, DHA, SA or a mixture thereof as the fatty acid, the resulting combination would be unworkable. As shown in the attached §1.132 Declaration of Dr. Kralovec, the reaction conditions disclosed by Mitchell do not result in the formation of esters. Substituting EPA, DHA or SA for the fatty acid of Mitchell would simply result in a mixture of phytosterol and the omega-3 fatty acid. No ester, as instantly claimed, would be formed.

Unexpected Results

Finally, Applicant reiterates the points made in Applicant's submission of July 15, 2002 that the instantly claimed nutritional supplement comprising a sterol ester of an omega-3 fatty acid overcomes significant problems in the prior art and does so with unexpected results. Referring again to the Declaration of H. Stephen Ewart, Ph.D. under 37 CFR 1.132 dated July 10, 2002 and submitted to the Patent Office with our submissions of July 15, 2002, Dr. Ewart describes that:

(1) A mere combination or mixture of a sterol and an omega-3 fatty acid results in a pasty composition that is not useful as a nutritional supplement in the form of either a food additive or a pharmaceutical composition.

(2) It was necessary to esterify the sterol to the omega-3 fatty acid to obtain a transparent, homogeneous oily liquid having properties useful as a nutritional supplement.

(3) Sterols, such as phytosterols, are not absorbed from the intestinal lumen into the bloodstream to any extent. Conversely, in order to have a triglyceride lowering effect, the omega-3 fatty acid must be absorbed from the intestinal lumen into the bloodstream. It was not known, prior to the present invention, whether the sterol component of the ester would prevent the omega-3 fatty acid from being absorbed into the bloodstream, negating its triglyceride lowering effect.

(4) The balance of scientific evidence is that omega-3 fatty acids, while having a triglyceride lowering effect, actually increase cholesterol levels. Therefore, it was unexpected that the cholesterol-increasing effect of the omega-3 fatty acid would not negate the cholesterol-lowering effect of the sterol.

Nevertheless, as discussed in the Declaration of H. Stephen Ewart dated March 27, 2001 and submitted with Applicant's paper of April 12, 2001, Applicant has found that the compositions of instant claim 1 do indeed unexpectedly reduce

both serum triglyceride and cholesterol levels.

In view of the foregoing, Applicant respectfully submits that the cited Mitchell, Mishkel *et al.* and Kamarei *et al.* references, either separately or in combination, do not teach or suggest a nutritional supplement comprising a sterol ester of an omega-3 fatty acid selected from DHA, EPA or SA as instantly claimed. Moreover, in view of the differing properties and mechanism of action of sterols and omega-3 fatty acids in regulating bloodstream cholesterol and triglyceride levels, it was unexpected and surprising that the nutritional supplements of the invention are useful for both lowering cholesterol and triglyceride levels in the bloodstream of a subject, as demonstrated by Applicant and as specified in the instant claims.

In view of the foregoing, entry of the amendments and further consideration of this application, leading to its timely allowance, are respectfully requested.

Respectfully submitted,

SMART & BIGGAR

By _____

David E. Schwartz
Reg. No. 48,211
Tel.: (613) 232-2486

Date: February 13, 2004

SMART & BIGGAR
P.O. Box 2999, Station D
900-55 Metcalfe Street
Ottawa, Ontario, Canada
K1P 5Y6

DES:srq